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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and antidepressant activity evaluation 2′-hydroxy-4′,6′-diisoprenyloxychalcone derivatives

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Abstract In this study, 14 2′-hydroxy-4′,6′-diisoprenyloxychalcone compounds were synthesized and their antidepressant activities were evaluated using the forced swimming test. The pharmacological results showed that six compounds significantly reduced immobility times during the forced swimming test at a dose of 10 mg/kg, indicative of antidepressant activity. Among these, three compounds (**4d**, **4e**, and **4g**) exhibited better antidepressant activity, with reduced immobility time by 38.3, 34.0, and 27.4 %, respectively. For explanation of the putative mechanism of action, compounds **4e**, **4g** were tested in chemical induced models.

Keywords 2′-Hydroxy-4′,6′-diisoprenyloxychalcone · Synthesis · Antidepressant activity · Chemical induced test

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Introduction

Depression is one of the most prevalent psychopathologies. Symptoms of depression include lowered mood and reduced interest and pleasure. It is predicted by the World Health Organization to become the second leading cause of disease-related disability by the year 2020 (Meyer, 2004; Lopez and Murray, 1998). Therefore, there is an unmet need for new antidepressant drugs.

Chalcones are the biogenetic precursors of all known flavonoids and are abundant in edible plants (Go *et al.*, 2005). They comprise open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. They have a broad spectrum of biological activities, such as anticancer, anti-inflammatory, antimalarial, antifungal, and antiviral(Batovska *et al.*, 2007; Lahtchev *et al.*, 2008; Trivedi *et al.*, 2007; Chimenti *et al.*, 2009).

In recent years, it has been reported that flavonoids possessed the antidepressant activities (Yi *et al.*, 2008; Wang *et al.*, 2008; Machado *et al.*, 2008; Paulke *et al.*, 2008; An *et al.*, 2008; Zhao *et al.*, 2011a). In our previous study, several differently substituted flavanone and chalcone derivatives exhibited the antidepressant activities. Among these, (4′-methoxy-5,7,3′-trihydroxyflavanone (compound **1**) and 2-bromo-2′,4′,6′-trihydroxychalcone (compound **2**) showed maximum antidepressant activity with significantly reduced times during the forced swimming test (FST) at a dose of 10 mg/kg (Zhao *et al.*, 2011a; Sui *et al.*, 2012) (Fig. 1).

The prenyl fragment is featured widely in many drugs and natural products (Zhao *et al.*, 2011b; Winans *et al.*, 1999).The isoamyl alkenyl group is an important group that exhibits a wide variety of pharmacological effects, for instance, anti-oxidative, anti-inflammatory, and anti-tumor (Vogel *et al.*, 2008, 2010; Rao *et al.*, 2009). In our search

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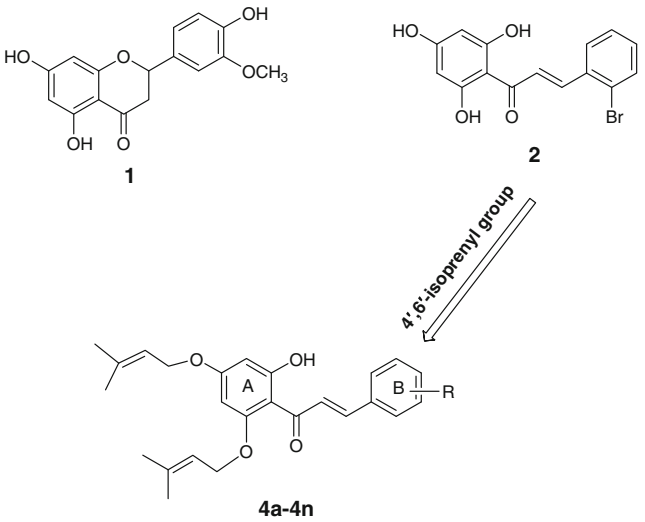


Fig. 1 Previous work compounds **1**, **2** and present study

for the new compounds with the antidepressant effects, introduction of an isoprenyl group to the 4′,6′-position on A-ring of compound **2** was carried out and led to the production of compounds **4a**–**4n**. The underlying hypothesis was that introduction of a substituted isoprenyloxy group would increase the lipophilic property of these compounds and increase their permeability across the blood–brain barrier, which would probably enhance their antidepressant activity (Fig. 1).

Reports on the antidepressant-like effects of the structural derivatives of 2′-hydroxy-4′,6′-diisoprenyloxychalcone are lacking. So a series of 2′-hydroxy-4′,6′-diisoprenyloxychalcone derivatives were designated and synthesized in this paper. The antidepressant activities of the synthesized compounds were also determined using the FST (Porsolt *et al.*, 1977; Porsolt, 1981) and the tail suspension test (TST) (Steru et al. 1985). The monoaminergic system is one of the most important targets in the pathophysiology and therapies for depression (Elhwuegi, 2004; Millan, 2004). Two behavioral models were used to investigate the possible monoaminergic participation in the antidepressant effect of the compounds **4e**, **4g**.

Experimental methods

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on an FT-IR1730 (Bruker, Switzerland); ^{1}H-NMR and ^{13}C-NMR spectras were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to tetramethylsilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Aldrich Chemical Corporation. All other chemicals were of the analytical grade.

*General procedure for the preparation of compounds (**4a**–**4n**)*

In a 100 mL round-bottomed flask, to a stirred solution of compounds **3a**–**3n** (substituted-2,4,6-trihydroxychalcone) (0.4 mmol) in 30 mL methanol and added to anhydrous K_2CO_3 (1.60 mmol) methanol solution. The mixture was stirred at 50 °C for 1 h, then was slowly added to prenyl bromide (0.58 mmol and 4 mL anhydrous acetone). The mixture was refluxed for 8–10 h after the completion of the reaction (monitored by TLC). K_2CO_3 was filtered and washed with acetone. After concentration under reduced pressure, the resultant was recrystallized from ethanol. The yield, melting point, and spectral data of each compound are given below.

*2′-Hydroxy-4′,6′-diisoprenyloxychalcone (**4a**)* Mp 76.4 °C; yield = 78.4 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.60 (s, 3H, –CH_3), 1.69 (s, 3H, –CH_3), 1.74 (s, 3H, –CH_3), 1.77 (s, 3H, –CH_3), 4.47 (d, 2H, –CH_2), 4.54 (d, 2H, –CH_2), 5.41 (*t*, 1H, =CH), 5.55 (*t*, 1H, =CH), 6.04–6.08 (m, 2H, –C_6H_2), 7.52 (d, 1H, J = 15 Hz, =CH), 7.19–7.36 (m, 5H, –C_6H_5), 8.02 (d, 1H, J = 15 Hz, =CH), 14.18 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.7, 18.9, 25.2, 25.4, 65.3, 65.6, 95.3, 97.1, 102.9, 121.6, 123.5, 123.9, 126.5, 126.8, 128.1, 128.4, 128.8, 132.1, 132.3, 135.4, 145.2, 163.5, 163.6, 168.6, 190.5; IR (KBr) cm^{-1}: 3314, 1645, 1589, 1220, 968; MS *m*/*z* 393 (M+1).

*4-Fluoro-2′-hydroxy-4′,6′-diisoprenyloxychalcone (**4b**)* Mp 101.2–102.1 °C; yield = 67.5 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.60 (s, 3H, –CH_3), 1.69 (s, 3H, –CH_3), 1.74 (s, 3H, –CH_3), 1.76 (s, 3H, –CH_3), 4.49 (d, 2H, –CH_2), 4.53 (d, 2H, –CH_2), 5.39 (*t*, 1H, =CH), 5.52 (*t*, 1H, =CH), 5.93–6.96 (m, 2H, –C_6H_2), 7.48 (d, 1H, J = 15 Hz, =CH), 7.02–7.76 (m, 4H, –C_6H_4), 7.80 (d, 1H, J = 15 Hz, =CH), 14.13 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.5, 18.7, 25.1, 25.5, 65.6, 65.8, 95.1, 96.9, 102.5, 114.9, 115.1, 121.2, 123.3, 123.7, 128.2, 128.5, 130.2, 132.1, 132.3, 145.5, 162.3, 163.6, 163.7, 168.7, 191.5; IR (KBr) cm^{-1}: 3313, 1645, 1586, 1220, 969; MS *m*/*z*411 (M+1).

*4–Chloro-2′-hydroxy-4′,6′-diisoprenyloxychalcone (**4c**)* Mp 117.5–119.2 °C; yield = 81.3 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.60 (s, 3H, –CH_3), 1.70 (s, 3H, –CH_3), 1.74 (s, 3H, –CH_3), 1.77 (s, 3H, –CH_3), 4.50 (d, 2H, –CH_2), 4.53 (d, 2H, –CH_2), 5.39 (*t*, 1H, =CH), 5.52 (*t*, 1H, =CH), 5.93-7.19 (m, 2H, –C_6H_2), 7.58 (d, 1H, J = 15 Hz, =CH), 7.20–7.43 (m, 4H, –C_6H_4), 7.94 (d, 1H, J = 15 Hz, =CH), 14.10 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.0,

19.1, 25.4, 25.7, 65.2, 65.3, 94.5, 95.6, 102.3, 121.5, 123.2, 123.9, 127.3, 127.5, 128.6, 128.8, 132.4, 132.6, 133.4, 133.9, 145.4, 163.3, 163.5, 168.8, 190.3; IR (KBr) cm^{-1}: 3312, 1644, 1585, 1220, 970; MS *m/z* 427 (M+1).

4-Bromo-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4d)*** Oil; yield = 85 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.59 (s, 3H, $–CH_3$), 1.68 (s, 3H, $–CH_3$), 1.74 (s, 3H, $–CH_3$), 1.78 (s, 3H, $–CH_3$), 4.46 (d, 2H, $–CH_2$), 4.51 (d, 2H, $–CH_2$), 5.45 (*t*, 1H, =CH), 5.54 (*t*, 1H, =CH), 5.92–6.03 (m, 2H, $–C_6H_2$), 7.56 (d, 1H, *J* = 15 Hz, =CH), 7.19–7.44 (m, 4H, $–C_6H_4$), 7.94 (d, 1H, *J* = 15 Hz, =CH), 14.11 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.1, 19.3, 25.6, 25.8, 65.1, 65.4, 93.5, 94.6, 102.5, 121.4, 122.5, 123.4, 123.6, 128.4, 128.6, 131.4, 131.7, 132.2, 132.4, 134.6, 145.6, 163.5, 163.7, 168.7, 190.2; IR (KBr) cm^{-1}: 3314, 1647, 1589, 1221, 970; MS *m/z* 471 (M+1).

2,4-Dichloro-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4e)*** Mp 98.9–99.4 °C; yield = 76 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.60 (s, 3H, $–CH_3$), 1.67 (s, 3H, $–CH_3$), 1.69 (s, 3H, $–CH_3$), 1.73 (s, 3H, $–CH_3$), 4.48 (d, 2H, $–CH_2$), 4.53 (d, 2H, $–CH_2$), 5.40 (*t*, 1H, =CH), 5.49 (*t*, 1H, =CH), 5.92-7.14 (m, 2H, $–C_6H_2$), 7.53 (d, 1H, *J* = 15 Hz, =CH), 7.20–7.43 (m, 3H, $–C_6H_3$), 7.93 (d, 1H, *J* = 15 Hz, =CH), 13.97 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.5, 19.6, 25.2, 25.6, 65.3, 65.5, 93.3, 94.9, 102.1, 121.6, 123.2, 123.7, 126.4, 129.6, 130.2, 131.3, 132.1, 132.3, 132.7, 134.8, 145.3, 163.6, 163.9, 168.8, 189.9; IR (KBr) cm^{-1}: 3313, 1645, 1587, 1220, 968; MS *m/z* 461 (M+1).

4-Methyl-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4f)*** Mp 95.2–96.3 °C; yield = 80.4 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.61 (s, 3H, $–CH_3$), 1.71 (s, 3H, $–CH_3$), 1.74 (s, 3H, $–CH_3$), 1.77 (s, 3H, $–CH_3$), 2.30 (s, 3H, $–CH_3$), 4.53 (d, 2H, $–CH_2$), 4.57 (d, 2H, $–CH_2$), 5.32 (*t*, 1H, =CH), 5.51 (*t*, 1H, =CH), 5.93-7.14 (m, 2H, $–C_6H_2$), 7.55 (d, 1H, *J* = 15 Hz, =CH), 7.18–7.50 (m, 4H, $–C_6H_4$), 7.91 (d, 1H, *J* = 15 Hz, =CH), 13.15 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.4, 19.6, 24.4, 25.5, 25.8, 65.4, 65.7, 93.8, 94.5, 102.4, 121.6, 123.6, 123.7, 126.4, 126.6, 129.4, 129.6, 132.1, 132.2, 132.5, 137.6, 145.3, 163.2, 163.6, 168.9, 190.4; IR (KBr) cm^{-1}: 3314, 1653, 1594, 1221, 970; MS *m/z* 407 (M+1).

4-Methoxyl-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4g)*** Oil; yield = 69.8 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.63 (s, 3H, $–CH_3$), 1.71 (s, 3H, $–CH_3$), 1.75 (s, 3H, $–CH_3$), 1.79 (s, 3H, $–CH_3$), 3.79 (s, 3H, $–OCH_3$), 4.48 (d, 2H, $–CH_2$), 4.56 (d, 2H, $–CH_2$), 4.93 (*t*, 1H, =CH), 5.54 (*t*, 1H, =CH), 6.63-7.19 (m, 2H, $–C_6H_2$), 7.57 (d, 1H, *J* = 15 Hz, =CH), 7.20-7.50 (m, 4H, $–C_6H_4$), 7.80 (d, 1H, *J* = 15 Hz, =CH), 13.10 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.1, 19.4, 25.2, 25.5, 55.5, 65.2, 65.5, 94.0, 95.1, 102.7, 114.3, 114.7, 121.2, 123.5, 123.8, 127.4, 127.6, 132.3, 132.6, 145.7, 159.6, 163.5, 163.7, 168.7, 190.7; IR (KBr) cm^{-1}: 3314, 1645, 1585, 1221, 970; MS *m/z* 423 (M+1).

4-Dimethylamine-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4h)*** Oil; yield = 75.7 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.63 (s, 3H, $–CH_3$), 1.72 (s, 3H, $–CH_3$), 1.75 (s, 3H, $–CH_3$), 1.78 (s, 3H, $–CH_3$), 2.98 (s, 3H, $–NCH_3$), 2.99 (s, 3H, $–NCH_3$), 4.29 (d, 2H, $–CH_2$), 4.48 (d, 2H, $–CH_2$), 4.87 (*t*, 1H, =CH), 4.90 (*t*, 1H, =CH), 6.58–7.19 (m, 2H, $–C_6H_2$), 7.76 (d, 1H, *J* = 15 Hz, =CH), 7.20-7.52 (m, 4H, $–C_6H_4$), 7.93 (d, 1H, *J* = 15 Hz, =CH), 13.29 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.7, 18.9, 25.6, 25.8, 40.4, 40.6, 65.0, 65.3, 94.2, 95.4, 102.3, 114.1, 114.4, 121.7, 123.6, 123.7, 127.1, 127.4, 132.0, 132.4, 145.1, 148.6, 163.0, 163.3, 168.9, 189.7; IR (KBr) cm^{-1}: 3316, 1652, 1586, 1221, 969; MS *m/z* 436 (M+1).

3-Methoxyl-2′,4-dihydroxy-4′,6′-diisoprenyloxychalcone ***(4i)*** Mp 70.5–72.9 °C; yield = 70.4 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.62 (s, 3H, $–CH_3$), 1.68 (s, 3H, $–CH_3$), 1.72 (s, 3H, $–CH_3$), 1.79 (s, 3H, $–CH_3$), 3.89 (s, 3H, $–OCH_3$), 4.49 (d, 2H, $–CH_2$), 4.86 (d, 2H, $–CH_2$), 5.23 (*t*, 1H, =CH), 5.37 (*t*, 1H, =CH), 6.67-7.15 (m, 2H, $–C_6H_2$), 7.56 (d, 1H, *J* = 15 Hz, =CH), 6.89-7.07 (m, 3H, $–C_6H_3$), 7.88 (d, 1H, *J* = 15 Hz, =CH), 13.11 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.3, 19.5, 25.3, 25.5, 55.8, 64.9, 65.3, 93.6, 94.9, 102.5, 112.1, 116.3, 120.8, 121.4, 123.3, 123.5, 128.4, 132.4, 132.6, 144.6, 145.6, 151.6, 163.2, 163.5, 168.8, 190.7; IR (KBr) cm^{-1}: 3310, 1648, 1587, 1220, 969; MS *m/z* 439 (M+1).

3-Nitro-2′-hydroxy-4′,6′-diisoprenyloxychalcone ***(4j)*** Mp 68.4–70.1 °C; yield = 64 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.61 (s, 3H, $–CH_3$), 1.68 (s, 3H, $–CH_3$), 1.75 (s, 3H, $–CH_3$), 1.78 (s, 3H, $–CH_3$), 4.48 (d, 2H, $–CH_2$), 4.52 (d, 2H, $–CH_2$), 5.42 (*t*, 1H, =CH), 5.54 (*t*, 1H, =CH), 5.94–7.07 (m, 2H, $–C_6H_2$), 7.54 (d, 1H, *J* = 15 Hz, =CH), 7.48–8.17 (m, 4H, $–C_6H_4$), 8.22 (d, 1H, *J* = 15 Hz, =CH), 14.15 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.6, 19.0, 25.3, 25.5, 65.3, 65.5, 93.5, 94.8, 102.5, 120.4, 121.2, 121.5, 123.6, 123.8, 129.7, 132.1, 132.3, 132.5, 136.6, 145.3, 148.7, 163.3, 163.5, 169.1, 191.4; IR (KBr) cm^{-1}: 3313, 1653, 1594, 1220, 965; MS *m/z* 438 (M+1).

2′-Hydroxy-4, 4′,6′-triisoprenyloxychalcone ***(4k)*** Mp 102.4–104.8 °C; yield = 83.2 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.60–1.92 (m, 18H, $–CH_3$), 4.42–4.50 (m, 6H, $–CH_2$), 5.40–5.45 (m, 3H, =CH), 5.93–7.19 (m, 2H, $–C_6H_2$), 7.46 (d, 1H, *J* = 15 Hz, =CH), 6.82–6.91 (m, 4H, $–C_6H_4$), 7.63 (d, 1H, *J* = 15 Hz, =CH), 14.13 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.6, 18.8, 19.3, 25.4, 25.6, 25.9, 65.0, 65.2, 65.7, 94.6, 95.8, 102.5, 114.3, 114.4, 121.5, 123.1,

123.3, 123.6, 127.2, 127.4, 127.6, 132.0, 132.1, 132.4, 145.3, 159.6, 163.3, 163.6, 170.1, 191.3; IR (KBr) cm^{-1}: 3312, 1652, 1590, 1221, 967; MS *m/z* 477 (M+1).

2′-Hydroxy-3,4,4′,6′-treisoprenyloxychalcone ***(4l)*** Oil; yield = 79 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.60–1.97 (m, 24H, $–CH_3$), 4.51–4.82 (m, 8H, $–CH_2$), 5.42–5.54 (m, 4H, =CH), 5.93–7.19 (m, 2H, $–C_6H_2$), 7.61 (d, 1H, *J* = 15 Hz, =CH), 6.78–7.09 (m, 3H, $–C_6H_3$), 7.82 (d, 1H, *J* = 15 Hz, =CH), 14.15 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.6, 18.7, 19.0, 19.3, 25.3, 25.5, 25.6, 25.8, 65.0, 65.3, 65.5, 70.2, 94.0, 95.1, 102.2, 111.4, 115.3, 119.6, 121.3, 123.0, 123.0, 123.7, 123.9, 128.6, 132.0, 132.1, 132.4, 132.6, 145.3, 148.3, 149.1, 149.8, 163.5, 163.7, 170.3, 191.6; IR (KBr) cm^{-1}: 3314, 1648, 1589, 1222, 966; MS *m/z* 561 (M+1).

3-(Furan-2-yl)-1-(2′-hydroxy-4′,6′-diisoprenyloxy)phenyl) prop-2-en-1-one ***(4m)*** Oil; yield = 61 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.61 (s, 3H, $–CH_3$), 1.69 (s, 3H, $–CH_3$), 1.73 (s, 3H, $–CH_3$), 1.76 (s, 3H, $–CH_3$), 4.47 (d, 2H, $–CH_2$), 4.50 (d, 2H, $–CH_2$), 5.45 (*t*, 1H, =CH), 5.56 (*t*, 1H, =CH), 6.07–7.14 (m, 2H, $–C_6H_2$), 7.48 (d, 1H, *J* = 15 Hz, =CH), 7.08–7.75 (m, 3H, –furan), 7.87 (d, 1H, *J* = 15 Hz, =CH), 14.10 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.3, 18.7, 24.7, 24.9, 65.1, 65.2, 94.6, 98.7, 101.2, 103.1, 111.1, 112.8, 123.1, 123.6, 127.5, 130.9, 131.4, 144.5, 152.6, 162.3, 163.8, 167.4, 190.2; IR (KBr) cm^{-1}: 3312, 1656, 1565, 1220, 961; MS *m/z* 383 (M+1).

1-(2′-Hydroxy-4′,6′-diisoprenyloxy)phenyl)-3-(naphthalen-2-yl)prop-2-en-1-one ***(4n)*** Mp 131.5–132.5 °C; yield = 84.7 %; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ1.61 (s, 3H, $–CH_3$), 1.69 (s, 3H, $–CH_3$), 1.71 (s, 3H, $–CH_3$), 1.75 (s, 3H, $–CH_3$), 4.04 (d, 2H, $–CH_2$), 4.48 (d, 2H, $–CH_2$), 5.42 (*t*, 1H, =CH), 5.54 (*t*, 1H, =CH), 5.93-7.07 (m, 2H, $–C_6H_2$), 8.06 (d, 1H, *J* = 15 Hz, =CH), 7.38–7.87 (m, 7H, –naphthalen), 8.55 (d, 1H, *J* = 15 Hz, =CH), 14.42 (s, 1H, –OH); ^{13}C-NMR ($CDCl_3$, 300 MHz): 19.1, 19.3, 25.1, 25.0, 65.6, 65.4, 93.4, 96.4, 103.3, 120.6, 121.5, 123.1, 123.4, 123.7, 125.5, 126.5, 126.8, 127.3, 128.3, 128.6, 132.4, 132.7, 133.4, 133.6, 145.5, 163.5, 163.7, 168.7, 190.4; IR (KBr) cm^{-1}: 3316, 1647, 1589, 1220, 965; MS *m/z* 443 (M+1).

Pharmacology

Forced swimming test (FST)

The FST used was the same as described in detail elsewhere by Porsolt (Porsolt *et al.*, 1977; Porsolt, 1981). The synthesized compounds were screened for their antidepressant activities. Local breed, male Kunming mice (20–24 g) were used in the FST under standard conditions with free access to food and water. They were housed in groups of six. On the test day, mice were dropped one at a time into a plexiglass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 22–25 °C. When testing, mice were assigned into different groups ($n = 10$ for each group). The synthesized compounds (10 mg/kg) and fluoxetine as a reference antidepressant drug (10 mg/kg) were dissolved in DMSO through injection intraperitoneally (ip) in a standard volume of 0.05 mL/20 g body weight, 30 min prior to the test. Then, the mice were dropped individually into the plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements in order to prevent sinking. The duration of immobility was recorded during the last 4 min of the 6 min test. Immobility period was regarded as the time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above the water. Following swimming sessions, they were then towel dried and returned to their housing condition. The animals were used only once in this test. All FSTs were performed between 10:00 a.m. and 18:00 p.m.

Tail suspension test (TST)

The TST was based on the method of Steru (Steru et al. 1985). Briefly, each mouse was individually suspended by its tail using a clamp (2 cm from the end) for 6 min in a box (25 × 25 × 30 cm) with the head 5 cm from the bottom. Testing was carried out in a darkened room with minimal background noise. On testing, mice were assigned into different groups ($n = 10$ for each group). The synthesized compounds (10 mg/kg) and fluoxetine as a reference antidepressant drug (10 mg/kg) were dissolved in DMSO injected ip in a standard volume of 0.05 mL/20 g body weight, 30 min prior to the test. After the first 2 min of the initial vigorous struggling, the animals were immobile. The duration of immobility was recorded during the last 4 min of the 6 min test. All test sessions were recorded by a video camera positioned directly above the box. Two competent observers blind to treatment scored the videotapes. Mice were considered immobile only when they hung passively and were completely motionless. The animals were used only once in this test. All TSTs were performed between 13:00 p.m. and 15:00 p.m.

5-Hydroxytryptophan (5-HTP) induced mouse head-twitch test

To investigate whether the serotonergic system was involved in the antidepressant-like effect of compounds **4e**, **4g**, we performed a 5-HTP-induced head-twitch test (Hanna

et al., 2007; Goodwin *et al.*, 1984). Totally 24 male Kunming (20–25 g) mice were randomly chosen and divided into three groups as normal control group, group of compounds **4e**, **4g**, and fluoxetine. Mice were administered an ip injection with compounds **4e**, **4g** (30 mg/kg), fluoxetine (30 mg/kg) and were dissolved in DMSO injected ip in a standard volume of 0.05 mL/20 g body weight, 60 min before 5-HTP (100 mg/kg, ip). Immediately after the second injection, mice were placed into plastic cages. Ten minutes later, the cumulative number of head twitches (rapid movements of the head with little or no involvement of the trunk) was recorded for 6 min. All test sessions were recorded by a video camera. The animals were used only once in this test; the head-twitch tests were performed between 13:00 p.m. and 16:00.

Yohimbine toxicity potentiation test

To reveal whether the noradrenergic system is involved in the antidepressant-like effect of compounds **4e**, **4g**, the yohimbine toxicity potentiation test was performed (Hanna *et al.*, 2007). Totally 40 male Kunming (20–25 g) mice were randomly chosen and divided into four groups: normal control group, group of compounds **4e**, **4g**, and clomipramine; compounds **4e**, **4g**, and clomipramine (30 mg/kg) were dissolved in DMSO injected ip in a standard volume of 0.05 mL/20 g body weight, 1 h prior to yohimbine administration (20 mg/kg, s.c.). The number of dead mice was calculated during a 24 h period after the injection of yohimbine.

Statistical analysis

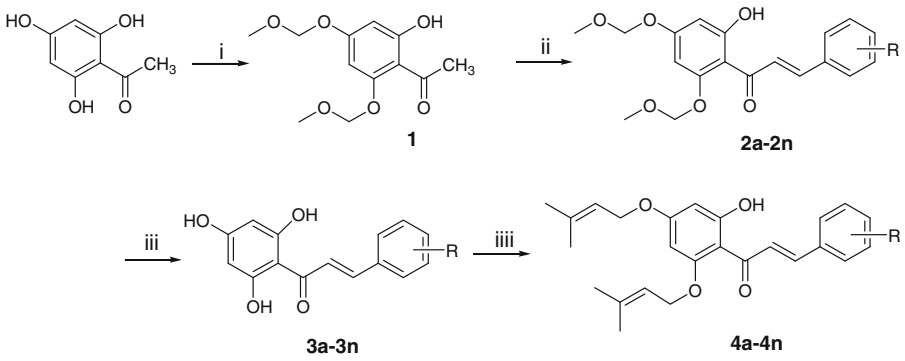
Results are expressed as mean ± SEM; *n* represents the number of animals. Data obtained from pharmacological experiments were analyzed with one-way analysis of variance (ANOVA) followed by Dunnet's post hoc test, using Pharmacologic Calculation System Version 4.1. (Microcomputer Specialists). A *p* value of less than 0.05 was considered statistically significant.

Results and discussion

Chemistry

The target compounds **4a**–**4n** were synthesized according to Scheme 1. Compound 1 was a key substrate for the subsequent reactions and was prepared by an established procedure (Sui *et al.*, 2012). Briefly, the starting material 1-(2,4,6-trihydroxyphenyl)ethanone reacted with chloro(methoxy)methane in acetone to yield compound **1**. Then, the intermediates **2a**–**2n** were synthesized by the Claisen–Schmidt condensation reaction from compound **1**, with appropriate aromatic aldehydes, protected as chloromethyl methyl ether in (Nishida *et al.*, 2007). Compounds **3a**–**3n** were obtained through the intermediates **2a**–**2n** reacted with 3 M HCl in methanol (Zhao *et al.*, 2005; 2010). Finally, the latter compounds subsequently underwent a substitution reaction with prenyl bromide in acetone on heating under reflux to give the title compounds **4a**–**4n**.

Scheme 1 Synthesis routes of target compounds **4a**–**4n**



R:

4a = H	4b = 4-F	4c =4-Cl	4d = 4-Br	4e = 2,4-Cl_2
4f = 4-CH_3	4g = 4-OCH_3	4h = 4-$N(CH_3)_2$	4i = 3-OCH_3-4-OH	4j = 3-NO_2
4k = 4-$OCH_2CH{=}C(CH_3)_2$	4l = 3,4-[$OCH_2CH{=}C(CH_3)_2$]$_2$	4m = 	4n = 	

Reagents and conditions:

(i) $ClCH_2OCH_3$, K_2CO_3, acetone; (ii) aromatic aldehyde, KOH, EtOH; (iii) 3 M HCl, MeOH; (iv) prenyl bromide, K_2CO_3 anhydrous, acetone.

Pharmacology

The FST and the TST were designed by Porsolt et al. and Steru et al. as primary screening tests for antidepressant activity and are behavioral tests used to predict the efficacy of antidepressant treatment (Porsolt *et al.*, 1977; Porsolt, 1981; Steru *et al.*, 1985). It remains one of the best models for this purpose for several reasons. It is used effectively in predicting the activity of a wide variety of antidepressant activities and is a low-cost, fast and reliable model to test potential antidepressant treatments with a strong predictive validity. The immobility time observed in the test reflects a state of lowered mood or hopelessness in animals; thus, these models are the most widely used tool for preclinical screening of the putative antidepressant agents and have good predictive value for antidepressant potency in humans (Bourin *et al.*, 2005; Petit-Demouliere *et al.*, 2005).

The performance of compounds **4a**–**4n** and the reference drug fluoxetine in the FST test are presented in Figs. 2 and 3. The pharmacological results exhibited that six compounds significantly reduced the duration of the immobility time at 10 mg/kg, compared with the control group showing better antidepressant activity. Acute treatment with compounds **4a**, **4d**–**4g**, and **4n** promoted a significant decrease in the immobility time in the FST at 10 mg/kg, as depicted in Fig. 2. (control = 116.7 ± 12.3; **4a** = 78.7 ± 18.8; **4d** = 72 ± 11; **4e** = 77.0 ± 8.9; **4f** = 79.3 ± 16.8; **4g** = 84.7 ± 8.3; **4n** = 73.3 ± 16.6; fluoxetine = 68.6 ± 8.3). The immobility time of mice treated with compounds **4b**, **4c**, **4h**–**4l**, and **4m** did not statistically differ from the control values as shown in Fig. 3 (control = 116.7 ± 12.3; **4b** = 97.7 ± 16.4; **4c** = 92.2 ± 16.2; **4h** = 110.8 ± 19.8; **4i** = 102.0 ± 15.5; **4j** = 98.5 ± 16.8; **4k** = 110.5 ± 16.8; **4l** = 96.8 ± 14.9; **4m** = 103.8 ± 15.6; fluoxetine = 68.6 ± 8.3).

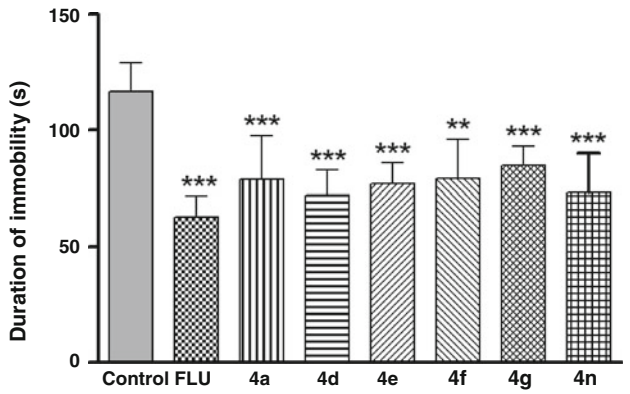


Fig. 2 Effects of the acute treatment with compounds (10 mg/kg) and FLU (10 mg/kg ip) on the immobility time in the forced swimming test. Each *column* represents the mean ± SEM. $^{**}p < 0.01$, $^{***}p < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test)

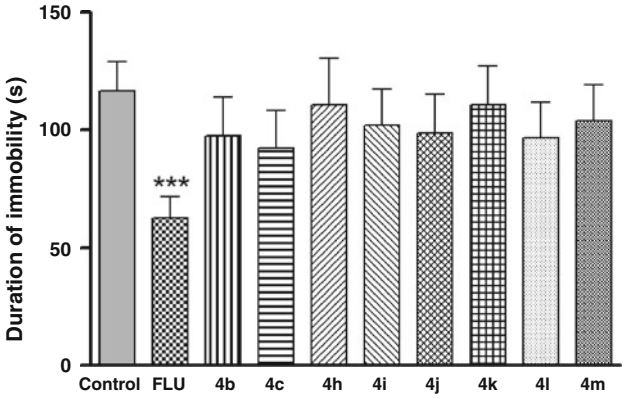


Fig. 3 Effects of the acute treatment with compounds (10 mg/kg) and FLU (10 mg/kg ip) on the immobility time in the forced swimming test. Each *column* represents the mean ± SEM. $^{*}p < 0.05$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test)

Among the derivatives, three compounds, **4d** (4-bromo-2′-hydroxy-4′,6′-diisoprenyloxychalcone), **4e** (2,4-dichloro-2′-hydroxy-4′,6′-diisoprenyloxychalcone), **4g** (4-methoxyl-2′-hydroxy-4′,6′-diisoprenyloxychalcone) were found to possess maximum antidepressant activity, and significantly reduced the duration of immobility times to 10 mg/kg dose level when compared to the control ($p < 0.001$), which reduced immobility time by 38.3, 34.0, and 27.4 %, respectively.

The structure–activity relationship of compounds **4a**–**4n** was analyzed using their activity in the FST test. Generally, the activity of an organic compound might be increased after the introduction of a halogen atom. So, some halogen-substituted derivatives were designed and synthesized in this paper. Analyzing the antidepressant activity of the synthesized compounds **4b**–**4e**, the following SAR was gained. The halogen-substituted derivatives (**4b**–**4e**), compounds except **4b**, **4e** displayed the antidepressant activity in the FST. The atom Br gave more contribution to the antidepressant activity than atoms F and Cl, the rank of the activity order of halogen-substituted derivatives was Br > F>Cl. Among these, compounds **4d** and **4e** showed maximum antidepressant activity in FST, with reduced immobility time by 38.3 and 34.0 % at 10 mg/kg, respectively. Next, the position of halogen substituted on the phenyl ring greatly influenced the antidepressant activity, compared with compounds with different Cl-substituted positions on phenyl ring; the rank of activity order was 2,4–Cl_2 > 4–Cl. The contribution order of the electron-donor group to the antidepressant activity (Fig. 2), is 4–OCH_3 > 4–CH_3 > –H > 4-N$(CH_3)_2$. However, introduction of an isoprenyl group to the 3,4-position on B-ring led to the production of compounds **4k**, **4l**, which did not show the antidepressant activity. In addition, compared with two aromatic heterocyclic compounds (**4m**, **4n**) were also designed and

synthesized. The pharmacological test revealed that the compound **4n** had better antidepressant activity at 10 mg/kg dose level compared with the control ($p < 0.01$) (Figs. 2, 3).

The immobility in the FST was significantly reduced after treatment with better activity compounds **4d**, **4e**, and **4g**, similar to the positive fluoxetine, as shown in Fig. 4, indicating a significant antidepressant-like effect. The decrease in immobility time in the TST showed similarity to that seen in the FST. Compounds **4d**, **4e**, and **4g** showed significantly the antidepressant activity and promoted a significant decrease in the immobility time at 10 mg/kg (control = 130.5 ± 9.6; **4d** = 106.3 ± 19.2; **4e** = 88.0 ± 16.6; **4g** = 86.7 ± 18.7; fluoxetine = 75.6 ± 8.3). Both FST and TST are the accepted stress models of depression. Immobility has been shown to reflect a state of 'behavioral despair and variants' or 'failure to adapt to stress' (Bourin *et al.*, 2005). Immobility displayed in both of these behavioral despair models has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in human. There was a significant correlation between clinical potency and the potency of antidepressant in both models. The compounds **4d**, **4e**, and **4g**, produced significantly antidepressant-like activity in both the FST and TST in mice, which indicates that compounds **4d**, **4e**, and **4g** possess some antidepressant effects.

In the present research, two behavioral models were used to investigate the possible monoaminergic participation of the effect of the antidepressant activity. Compounds **4e** and **4g**, as the most active compounds, were chosen for these tests. Compounds **4e** and **4g** increased significantly the cumulative number of head twitches ($p < 0.05$ vs. control) in the 5-HTP-induced mouse head-twitch test, whereas they enhance the mouse lethality ($p < 0.05$ vs. control) induced by yohimbine. The results indicated that the serotonergic, but not the noradrenergic system, was involved in the antidepressant-like effect of compounds **4e** and **4g** (Tables 1, 2).

Several lines of evidence indicate that serotonergic, dopaminergic, and noradrenergic neurotransmissions are involved in the expression of the antidepressant-like effect in the behavioral despair models of depression (Schechter *et al.*, 2005). Many antidepressant drugs exert their effects by modulating those neurotransmission system (Richelson, 2002; Corne *et al.*, 1963). The 5-HTP-induced mouse head-twitch test is an effective method to evaluate serotonergic effects of drugs in vivo (Lapin, 1980). It has been generally accepted that numbers of head twitches represent the level of 5-HT in the synapses. Yohimbine, an a_2-adrenergic release by its antagonistic action on the presynaptic a_2-adrenoceptor. The yohimbine toxicity potentiation test is usually used for the evaluation of noradrenergic effect of antidepressants (Deng *et al.*, 2012).

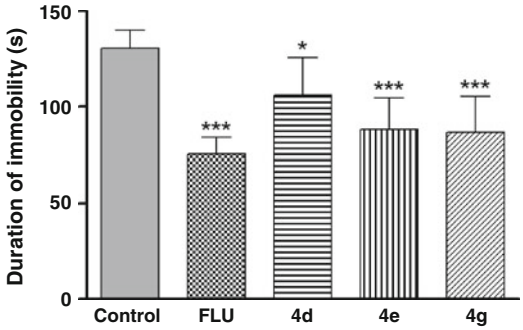


Fig. 4 Immobility time of compounds **4d**, **4e**, and **4g** in mouse TST. Data expressed as mean ± SEM ($n = 10$). Statistical analysis of data was carried out by one-way analysis of variance followed by the *t* test. *$p < 0.05$, ***$p < 0.001$ vs. control

Table 1 Effects of compound **4e**, **4g** and fluoxetine on the number of 5-HTP-induced head twitches in mice

Compounds	Dose (mg/kg)	5-HTP (mg/kg)	Number of head twitches
4e	30	100	36.5 ± 12.4*
4g	30	100	38.1 ± 10.7*
Fluoxetine	30	100	42.7 ± 11.3**
Control	–	100	15.7 ± 5.2

Values are the mean ± SEM. ($n = 10$)

Significantly different compared with control (Dunnett's test: *$p < 0.05$, **$p < 0.01$)

Table 2 Effects of compounds **4e**, **4g** and clomipramine on yohimbine-induced toxicity (mortality) in mice

Compound	Dose (mg/kg)	Yohimbine (mg/kg)	Lethality	
			Total	Mortality (%)
4e	30	20	10	70*
4g	30	20	10	60*
Clomipramine	30	20	10	80*
Control	–	20	10	20

Values are the mean ± SEM. ($n = 10$)

Significantly different compared with control (Fisher's exact test: *$p < 0.05$)

Conclusion

In conclusion, a series of 2′-hydroxy-4′,6′-diisoprenyloxychalcone derivatives were synthesized and their antidepressant activities were evaluated using the FST. The pharmacological results showed that six compounds significantly reduced immobility times during the FST at 10 mg/kg, thereby suggesting the antidepressant activity. Among these, three compounds **4d**, **4e**, and **4g** showed better antidepressant activity. In addition, in the 5-HTP-induced

head-twitch test and yohimbine-induced mortality test, compounds **4e** and **4g** could increase the rate of head-twitching and increase the prevalence of mortality. The mechanism of the action of the antidepressant effects may be related to 5-HT and NE. Further studies should be initiated to reveal the mechanism of action of the antidepressant-like effect of compounds **4e** and **4g**.

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